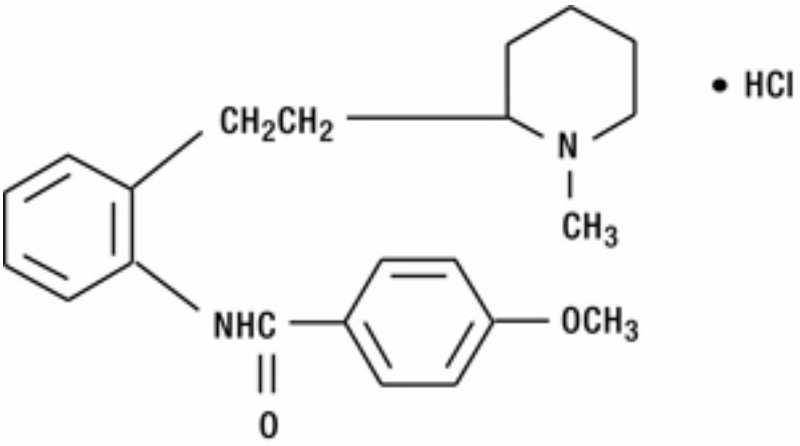
ENKAID - encainide hydrochloride capsule, gelatin coated
Bristol-Myers Squibb Company

DESCRIPTION

ENKAID® (encainide hydrochloride) is an antiarrhythmic drug supplied as 25 and 35 mg capsules for oral administration. The chemical name of ENKAID is (±)-4-methoxy-N-[2-[2-(1-methyl-2-piperidinyl)ethyl]phenyl] benzamide monohydrochloride. Its molecular weight is 388.94 and the structural formula is represented as follows:



Encainide hydrochloride is a white solid which is freely soluble in water, slightly soluble in ethanol, and insoluble in heptane. The pH of a 1% aqueous solution is 5.8. In addition to the hard gelatin capsule shell, the other inactive ingredients are lactose, magnesium stearate and sodium starch glycolate.

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanisms of the antiarrhythmic effects of ENKAID are unknown but probably are the result of its ability to slow conduction, reduce membrane responsiveness, inhibit automaticity, and increase the ratio of the effective refractory period to action potential duration. ENKAID produces a differentially greater effect on the ischemic zone as compared with normal cells in the myocardium. This could result in the elimination of the disparity in the electrophysiologic properties between these two zones and eliminate pathways of abnormal impulse conduction, development of boundary currents and/or sites of abnormal impulse generation.

Electrophysiology

ENKAID is a Class IC antiarrhythmic agent, ie, is a blocker of the sodium channel of Purkinje fibers and the myocardium.
In isolated Purkinje and myocardial cells its electrophysiologic profile is characterized by a dose-related slowing of phase 0 depolarization and little effect on either the action potential duration or repolarization. This profile differs from that of Class IA drugs (eg, quinidine, disopyramide, procainamide) that slow phase 0 depolarization and prolong action potential duration or Class IB agents (eg, lidocaine, tocainide and mexiletine) that slow phase 0 depolarization only slightly and shorten the action potential duration.
In the intact animal and man, the electrophysiologic effects of encainide are a result not only of encainide but of two metabolites as well, each of which is present in most patients (over 90%) at therapeutically active levels. Encainide and its metabolites produce a dose-related decrease in intracardiac conduction in all parts of the heart, with slowing of conduction in the His-Purkinje system and AV node and an increase in the refractoriness of the atrium and ventricle. (See **WARNINGS: Electrocardiographic Changes**.)
Each variable studied in normal and ischemic tissues is altered in the same manner in both, but more markedly in ischemic tissues.
ENKAID has also been shown to slow conduction and increase refractoriness in accessory atrioventricular pathways and in the AV node.

HEMODYNAMICS

In oral studies of hemodynamic effects, using invasive and noninvasive measurements of cardiac function. ENKAID had no effects on measurements of cardiac performance such as cardiac or stroke volume index, pulmonary capillary wedge pressure or peripheral blood pressure either at rest or during exercise. In noninvasive studies that included both geriatric patients and younger patients with impaired left ventricular function (New York Heart Association Class III & IV) there were no detrimental effects on ejection fractions acutely or after more than 12 months of therapy in some cases. Doses of 75-300 mg/day of ENKAID, which reduced the incidence of premature ventricular complexes by at least 80%, did not adversely affect exercise tolerance, and were well tolerated clinically by patients with markedly impaired left ventricular function. In a few instances, however, apparent new or worsened congestive heart failure has developed during treatment with ENKAID (See **WARNINGS**).

CLINICAL ACTIONS

Although ENKAID should not be used for the treatment of nonlife-threatening arrhythmias, in premarketing, placebo-controlled trials ENKAID caused a dose-related reduction in the occurrence of single, repetitive and multiform premature ventricular complexes. ENKAID has been shown to reduce the incidence of nonsustained ventricular tachycardia. Doses of 75-150 mg per day were needed in most patients to attain 75% or greater suppression. In programmed electrical stimulation studies, ENKAID has prevented the induction of ventricular tachycardia in about 20% to 30% of the patients. ENKAID has also been shown to reduce the recurrence of sustained ventricular tachycardia in patients with a history of malignant arrhythmias.

ENKAID is effective in treating ventricular arrhythmias in patients with and without organic heart disease and has frequently been effective in patients who were unresponsive to, or intolerant of, one or more other antiarrhythmic agents.

When ENKAID therapy was discontinued, such as during placebo phases in the premarketing clinical trials, ventricular ectopy returned to rates that did not differ significantly from the baseline values. That is, no clinical evidence of arrhythmia exacerbation or "rebound" has been noted following discontinuation.

PHARMACOKINETICS

The absorption of ENKAID after oral administration is nearly complete with peak plasma levels present 30 to 90 minutes after dosing. There are two major genetically determined patterns of encainide metabolism. In over 90% of patients the drug is rapidly and extensively metabolized with an elimination half-life of 1 to 2 hours. These patients convert encainide to two active metabolites, O-demethylencainide (ODE) and 3-methoxy-O-demethylencainide (MODE), that are more active (on a per mg basis) than encainide itself. These metabolites are eliminated more slowly than encainide, with half-lives of 3 to 4 hours for ODE and 6-12 hours for MODE. A radiolabeled dose of encainide is excreted in approximately equal amounts in the urine and feces. A major urinary metabolite is ODE, with lesser amounts of encainide and MODE present.

In less than 10% of patients, metabolism of encainide is slower and the estimated encainide elimination half-life is 6 to 11 hours. Slow metabolism of encainide is associated with a diminished ability to metabolize debrisoquin. In these patients the renal excretion of encainide is a major route of elimination and little if any MODE and only small amounts of ODE are present in their plasma.

Despite the differences in pharmacogenetics, in all patients 3 to 5 days of dosing are required to achieve steady state conditions. Based on clinical experience and pharmacokinetic considerations, the recommended dosage regimen (see **DOSAGE AND ADMINISTRATION**) is appropriate for all patients regardless of their genetically determined capacity to metabolize encainide.

Encainide, ODE, and MODE follow a nonlinear pharmacokinetic disposition, although ODE and MODE differ from linearity only to a small extent. The absorption of ENKAID is retarded by food, but the overall bioavailability is not altered. The pharmacokinetics of ENKAID do not change with increasing age over 21, and are not different between men and women.

The clearance of encainide and conversion to active metabolites is reduced in patients with hepatic disease, but serum concentrations of ODE and MODE are similar to those in normal patients. There is insufficient experience to be certain about the need for alteration in the normal dose and/or dosing interval when ENKAID is administered to patients with hepatic disease, but it is prudent to increase doses cautiously.

The clearance of encainide is reduced, and plasma levels of the active metabolites ODE and MODE are increased in patients with significant renal impairment and the dosage should be reduced in these patients (see **PRECAUTIONS**).

Encainide and ODE are bound to a moderate extent to plasma proteins (75%-85%) while the binding of MODE, at about 92%, is somewhat greater.

For information on potential drug interactions see **PRECAUTIONS: Drug Interactions.**

INDICATIONS AND USAGE

ENKAID is indicated for the treatment of documented ventricular arrhythmias such as sustained ventricular tachycardia that, in the judgement of the physician, are life-threatening. Because of the proarrhythmic effects of ENKAID, its use should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks. ENKAID should not be used in patients with less severe ventricular arrhythmias, even if the patients are symptomatic.

Treatment with ENKAID should be initiated in a hospital. Patients should also be hospitalized at the time of a dose increase to 200 mg per day or above (see **DOSAGE AND ADMINISTRATION**).

The effects of ENKAID in patients with supraventricular arrhythmias and patients with recent myocardial infarction (except as described in the **WARNINGS** section) have not been adequately studied.

As is the case for other antiarrhythmic agents, there is no evidence from controlled trials that the use of ENKAID favorably affects survival or the incidence of sudden death.

CONTRAINDICATIONS

ENKAID is contraindicated in patients with preexisting second- or third-degree AV block, or with right bundle branch block when associated with a left hemiblock (bifascicular block), unless a pacemaker is present to sustain the cardiac rhythm should complete heart block occur. ENKAID is also contraindicated in the presence of cardiogenic shock or known hypersensitivity to the drug.

WARNINGS

Mortality

ENKAID was included in the National Heart Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multi-center, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had a myocardial infarction more than six days but less than two years previously. An excessive mortality or nonfatal cardiac arrest rate was seen in patients treated with ENKAID compared with that seen in patients assigned to a carefully matched placebo-treated group. This rate was 40/415 (9.6%) for ENKAID and 15/416 (3.6%) for the matched placebo. The average duration of treatment with ENKAID in this study was ten months.
The applicability of the CAST results to other populations (e.g., those without recent myocardial infarction) is uncertain, but at present it is prudent to consider the risks of Class 1c agents (including ENKAID), coupled with the lack of any evidence of improved survival, generally unacceptable in patients without life-threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life-threatening, symptoms or signs.

Proarrhythmia
ENKAID, like other antiarrhythmic agents, can cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia; eg, tachycardia that is more sustained or more resistant to conversion to sinus rhythm, with potentially fatal consequences.
In patients with malignant arrhythmias, it is often difficult to distinguish a spontaneous variation in the patient's underlying rhythm disorder from drug induced worsening, so the following occurrence rates must be considered approximations.
Overall, in premarketing clinical trials with ENKAID about 10% of all patients had proarrhythmic events, about 6% of them representing new or worsened ventricular tachycardia. Provocation or aggravation occurred most frequently in patients who had a history of sustained ventricular tachycardia (12% of such patients), cardiomyopathy (16%), congestive heart failure (12%), or sustained ventricular tachycardia with cardiomyopathy or congestive heart failure (17%). The incidence of proarrhythmic events in patients without ventricular tachycardia or overt manifestations of clinical heart disease ranged from 3% to 4%. Proarrhythmia occurred least frequently in patients with no known structural heart disease. Age, sex, baseline ECG intervals, or ECG changes caused by ENKAID were not predictive of the occurrence of proarrhythmia.
A review of deaths in premarketing clinical trials indicates that about 1% of patients might have died of a possible proarrhythmic effect of ENKAID, virtually all of them patients with a history of ventricular tachycardia. In most cases, patients had a history of sustained ventricular tachycardia or ventricular fibrillation.
Proarrhythmic events in premarketing clinical trials occurred most commonly during the first week of therapy and were much more common when doses exceeded 200 mg/day. Initiating therapy at 75 mg/day combined with gradual dose adjustment reduced the risk of proarrhythmia (see DOSAGE AND ADMINISTRATION).

Congestive Heart Failure
New or worsened congestive heart failure (CHF) attributed to ENKAID occurred infrequently (< 1%); nevertheless, ENKAID should be used cautiously in patients with CHF or congestive cardiomyopathy.

Electrolyte Disturbances
Hypokalemia or hyperkalemia may alter the effects of Class I antiarrhythmic drugs. Preexisting hypokalemia or hyperkalemia should be corrected before administration of ENKAID.

Sick Sinus Syndrome — (Bradycardia-Tachycardia Syndrome)
ENKAID should be used only with extreme caution in patients with sick sinus syndrome because it may cause sinus bradycardia, sinus pause, or sinus arrest.

Electrocardiographic Changes
ENKAID slows conduction and consequently produces dose-related changes in the PR and QRS intervals. The intervals increase in a linear manner at doses from 30 to 225 mg/day. There is no consistent change in the JT. The QTc interval is increased, but only to the extent of the increase in QRS interval.

Changes in ECG Intervals*

Total Daily Dose (mg)						
	75		150		200	
Interval	**sec**	**(%)**	**sec**	**(%)**	**sec**	**(%)**
PR	0.02	(12)	0.04	(21)	0.04	(24)
QRS	0.01	(12)	0.02	(23)	0.02	(26)

*Percent change based on mean baseline values of PR = 0.169 and QRS = 0.088 from a group of 504 patients treated for ventricular arrhythmias.

Unlike the changes in the PR, QRS, and QTc intervals observed with the Class IA drugs, the ECG changes induced by ENKAID are not in themselves indications of effectiveness, toxicity or overdosage nor can they routinely be used to predict efficacy.
Clinically significant changes in cardiac conduction have been observed. Sinus bradycardia, sinus pause, or sinus arrest occurred in 1% of the patients and prolongation of QRS interval to greater than/or equal to 0.20 sec developed in about 7% of the patients. The incidence of second- or third-degree AV block was less, 0.5% and 0.2% respectively.

Effects on Pacemaker Thresholds
The safety of ENKAID in patients with permanently implanted programmable pacemakers has been established in a small (10 patient) study which evaluated the effects of increasing doses on pacemaker thresholds. ENKAID has a limited potential for increasing pacemaker thresholds. Only one subject had a clinically significant change that would require pacemaker reprogramming and that occurred only at the highest dose tested (75 mg t.i.d.). These effects were reversed when the drug was discontinued. It is advisable to establish pacemaker threshold prior to encainide administration and at regular intervals during therapy. Reprogramming of multi-programmable pacemakers may be required to increase voltage or pulse width. ENKAID should not be administered to patients with existing poor thresholds or nonprogrammable pacemakers unless suitable pacing rescue is available. In addition to possible rise in pacing threshold, ENKAID may suppress ventricular escape rhythms.

PRECAUTIONS

Drug Interactions
In prospective studies single and multiple doses of ENKAID have had no significant effect on serum digoxin levels. Likewise, combined digoxin/ENKAID therapy has been administered without adverse effects.
Experience has indicated no obvious problems with the combined use of ENKAID and other antiarrhythmic agents, diuretics, beta blockers or calcium channel blockers. However, because of possible additive pharmacologic effects, caution is indicated when ENKAID is used with another antiarrhythmic agent or any other drug that affects cardiac conduction.
Cimetidine (300 mg q.i.d.) increases plasma concentrations of encainide and its active metabolites. Although no clinically significant consequences have been reported, caution should be utilized when the two drugs are administered simultaneously. ENKAID dosage should be reduced if cimetidine is to be given to a patient taking ENKAID.
In vitro binding studies with several drugs that may be administered concomitantly have not revealed any significant alteration in the protein binding of encainide, ODE, or MODE; nor did high concentrations of encainide and its metabolites alter the binding of the other medications including such highly protein bound drugs as warfarin.

Hepatic Impairment
Patients with hepatic impairment have a significantly reduced rate of elimination of encainide, probably as a consequence of decreased metabolism to ODE and MODE; serum concentrations of ODE and MODE, however, are little altered. There is insufficient experience to be certain about the need for alterations in the dose and/or dosing interval of ENKAID in patients with hepatic disease, but it is prudent to increase doses cautiously.

Renal Impairment
Limited data suggest that reduction in the elimination of encainide and its active metabolites ODE and MODE in patients with severe renal impairment (serum creatinine > 3.5 mg/dL or creatinine clearance of less than 20 mL/min) results in significant accumulation of metabolites and, to a lesser degree, encainide. In such patients, therapy with ENKAID should be initiated with a single daily dose of 25 mg. If needed the dose may be increased to 25 mg b.i.d. after at least 7 days, and again to 25 mg t.i.d. after an additional 7 days if necessary. Doses above 150 mg per day are not recommended. Consideration should be given to reducing ENKAID dosage if renal function deteriorates significantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity studies have been performed by the oral route in rats and mice at doses up to 30 mg/kg/day and 135 mg/kg/day, respectively. No drug-related increase in tumor incidence was observed. Bacterial and mammalian mutagenicity tests with encainide have been negative. No reduction in fertility occurred in rats at oral doses up to 14 mg/kg/day. Fertility was reduced when both male and female rats received oral doses of 28 mg/kg/day (approximately 13 times the average human dose) prior to mating; there was no reduction with treatment of each sex separately at the same dose.

Pregnancy Category B
Reproduction studies have been performed in rats and rabbits at doses up to 13 and 9 times the average human dose, respectively, and have revealed no evidence of harm to the fetus due to encainide. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
Encainide is excreted in the milk of laboratory animals and has been reported to be present in human milk. Although no overt postnatal effects were observed in the postnatal phase of the rodent reproduction studies, other than decreased weight at the highest

dose of 28 mg/kg/day (13 times human dose), the potential for serious adverse reactions in nursing infants from ENKAID is unknown. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
The safety and effectiveness of ENKAID (encainide hydrochloride) in pediatric patients have not been established.

ADVERSE REACTIONS
In the National Heart Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), the incidence of total mortality and nonfatal cardiac arrest in the ENKAID group was 40/415 (9.6%) and that in the placebo group was 15/416 (3.6%). (See boxed**WARNINGS**). The most serious adverse reactions reported for ENKAID in premarketing clinical trials were the provocation or aggravation of ventricular arrhythmias (See **WARNINGS**). These occurred during the course of the clinical research program in about 10% of the patients who received a wide range of doses under a variety of circumstances. In some cases this resulted in the development of sustained ventricular tachycardia or ventricular fibrillation.
Only 0.4% of patients discontinued ENKAID therapy due to congestive heart failure or related causes. Second- or third-degree AV block developed in 0.5% and 0.2% of the patients, respectively. Sinus bradycardia, sinus pause or sinus arrest occurred in 1% of patients. There have been rare reports of elevated serum liver enzymes (alkaline phosphatase, serum transaminase), hepatitis, and jaundice, in which a relation to encainide is possible and there has been one instance of a rechallenge-confirmed elevation of transaminases. There have also been rare reports of elevated blood glucose levels or of increased insulin requirements in diabetic patients. Although no cause and effect relationship has been established, caution is advised in patients who develop unexplained jaundice or signs of hepatic dysfunction or hyperglycemia and consideration should be given to discontinuing therapy.
In premarketing evaluations, 2400 subjects were exposed to ENKAID, of whom more than 500 were maintained on drug for two years or longer. Adverse events were sufficiently troublesome to cause discontinuation in about 7% of the patients participating in premarketing clinical trials. The most frequently reported adverse events were dizziness, blurred or abnormal vision, and headache.
The following table lists the most common adverse events that occurred in two multi-center premarketing clinical trials, one of which compared encainide to placebo, the other to quinidine. This table lists all such adverse events reported by at least 3% of the patients and thus may include symptoms of the underlying disease, intercurrent illness or adverse reactions to drug therapy.
Incidence (%) of Adverse Events

	Encainide/Placebo Trial		**Encainide/Quinidine Trial**	
Body System	**Encainide (N = 88)**	**Placebo (N = 37)**	**Encainide (N = 153)**	**Quinidine (N = 154)**
Body as a Whole				
abdominal pain	2.3	0	1.3	3.9
asthenia	14.8	16.2	6.5	13.6
chest pains	10.2	8.1	8.5	8.4
death	3.4	0	1.3	0
fever	–	–	0	7.8
headache	5.7	5.4	8.5	15.6
lower extremity pain	5.7	0	4.6	5.2
malaise	–	–	0	3.9
upper extremity pain	4.5	5.4	2.0	3.9
Cardiovascular				
palpitations	12.5	18.9	7.2	5.8
peripheral edema	2.3	0	1.3	3.2
proarrhythmia	3.4	0	0.7	0.6
Digestive				
constipation	2.2	0	4.6	2.6
diarrhea	0	8.1	9.2	39.0
dry mouth	–	–	3.9	2.6
dyspepsia	5.7	5.4	4.6	9.7
nausea	2.3	2.7	8.5	10.4
vomiting	2.3	0	0.7	3.2
Nervous				
anorexia	1.1	0	2.0	3.2
dizziness	15.9	10.8	15.7	14.9

insomnia	3.4	0	2.0	1.3
nervousness	1.1	0	2.0	3.2
somnolence	–	–	3.9	1.9
Respiratory				
dyspnea	8.0	10.8	3.9	8.4
Skin and Appendages				
rash	1.1	0	2.0	4.5
Special Senses				
abnormal/blurred vision	3.4	2.7	11.1	5.8
tinnitus	–	–	3.9	3.9

The following table gives the incidence of the most common adverse events at selected doses of ENKAID that were used during the premarketing clinical trials which involved a total of 749 patients with ventricular arrythmias. The incidence figures in the “0 mg” column are based on events that occurred while patients were on placebo or in drug-free wash out periods.
Incidence (%) of the Most Common Adverse Events at Various Doses (Includes all adverse events regardless of relationship to drug therapy.)

	Daily Doses			
Body System	**0 mg (N = 479)**	**75 mg (N = 298)**	**150 mg (N = 260)**	**> 200 mg (N = 208)**
Body as a Whole				
abdominal pain	1	2	2	3
asthenia	4	4	5	9
chest pain	3	5	2	6
headache	6	3	5	12
lower extremity pain	3	< 1	1	3
upper extremity pain	1	< 1	< 1	2
pain	< 1	< 1	< 1	< 1
paresthesia	< 1	1	< 1	2
Cardiovascular				
congestive heart failure	< 1	< 1	1	2
palpitations	5	4	3	8
premature ventricular contraction	< 1	< 1	< 1	3
QRS interval prolonged ≥ 0.20	< 1	< 1	3	4
syncope	< 1	< 1	1	5
ventricular tachycardia	< 1	3	3	8
Digestive				
constipation	1	< 1	< 1	2
diarrhea	2	< 1	< 1	2
dyspepsia	1	< 1	< 1	3
nausea	2	2	2	6
Nervous				
dizziness	7	6	10	18
tremor	< 1	< 1	< 1	2
Respiratory				
dyspnea	2	2	5	4
increased cough	< 1	< 1	1	2
Skin and Appendages				
rash	2	< 1	< 1	4
Special Senses				

abnormal/blurred vision	5	4	8	26
taste perversion	< 1	1	2	1

Other adverse events occurring in less than 1% of the patients receiving ENKAID include: malaise, decreased or increased blood pressure, confusion, ataxia, abnormal gait, abnormal sensation, abnormal dreams, diplopia, photophobia and periorbital edema.

POSTINTRODUCTION CLINICAL EXPERIENCE

Other than the clinical experience in the CAST study described above (see boxed **WARNINGS** and **ADVERSE REACTIONS**), postmarketing experience has shown an adverse experience profile similar to that described for the premarketing clinical trials. Voluntary reports since introduction include rare reports (less than one report per 10,000 patients) of arthralgia, fever, leukopenia, positive ANA test, and thrombocytopenia. Because of the uncontrolled nature of these voluntary reports, and because most of the patients were receiving concomitant medications, any causal relationship to ENKAID treatment is difficult to establish.

OVERDOSAGE

Intentional or accidental overdosages with ENKAID have resulted in death.

Signs, Symptoms, and Laboratory Findings Associated with an Overdosage of the Drug

Overdosage with ENKAID may produce excessive widening of the QRS complex and QT interval and AV dissociation. Hypotension, bradycardia and finally asystole may develop. A variety of conduction disturbances may be observed. Convulsions have occurred in one case of intentional overdosage.

Oral LD_{50} of the Drug in Animals

The acute, oral LD_{50} values for encainide are estimated to be 80 mg/kg in the mouse and 59 mg/kg in the rat.

Recommended General Treatment Procedures

In the event of overdosage with ENKAID, patients should be hospitalized and provided with cardiac monitoring and advanced life support systems. No specific antidote for ENKAID has been identified; however, one report has suggested hypertonic sodium bicarbonate may be useful in managing the cardiac toxicity associated with an ENKAID overdosage. Acute overdosages should be treated by gastric lavage followed by activated charcoal. Treatment of overdosage should be supportive.

DOSAGE AND ADMINISTRATION

As with other antiarrhythmic agents, ENKAID therapy in patients with sustained ventricular tachycardia should be initiated in a hospital setting with facilities for cardiac rhythm monitoring. Hospitalization is also recommended for patients with sinus node dysfunction or cardiomyopathy and/or congestive heart failure even if there is no history of sustained ventricular tachycardia, and at the time of a dose increase to 200 mg per day or above.

ENKAID should be administered only after appropriate clinical assessment and the dosage of ENKAID must be individualized for each patient on the basis of therapeutic response and tolerance.

The recommended initial dosing schedule for adults is one 25 mg ENKAID capsule t.i.d. at approximately 8-hour intervals. After a period of 3 to 5 days, the dosage may be increased to 35 mg t.i.d. if necessary. If the desired therapeutic response is not achieved after an additional 3 to 5 days, the dose may again be adjusted to 50 mg t.i.d. Rapid dose escalation should be avoided.

Patients with hepatic disease or severe renal impairment may require dose and/or dosing interval adjustment (See **PRECAUTIONS**).

Dosages of ENKAID should be adjusted gradually allowing 3 to 5 days between dosing increments.

This will allow all patients (even the minority that metabolize the drug very slowly), to achieve “steady state” blood levels of encainide and its active metabolites before increasing the dose. Gradual dose adjustments will help prevent the usage of doses which are higher than necessary to control the arrhythmia and which may increase the risk of proarrhythmic events.

In an occasional patient, the dosage may have to be increased to 50 mg q.i.d. to achieve the desired therapeutic response. Higher doses are not normally recommended. However, after the careful dose titration as described above has failed, patients with documented life-threatening arrhythmias may be treated with up to 75 mg q.i.d. Patients should be hospitalized at the time of these dose increases to 200 mg per day or above. Once the desired therapeutic response is achieved, many patients can be adequately maintained on chronic therapy at doses lower than the maximum achieved during titration.

Patients with malignant arrhythmias who exhibit a beneficial response as judged by objective criteria (Holter monitoring, programmed electrical stimulation, exercise testing, etc.) can be maintained on chronic ENKAID therapy.

Some patients whose arrhythmias are well controlled by dosages of 50 mg t.i.d. or less may be transferred to a 12-hour dosage regimen if necessary to increase convenience and help assure compliance. Only those patients who have had an adequate response to 50 mg t.i.d. or less should be transferred to a 12-hour dosage regimen. The total daily dose may be given in two equally divided doses at approximately 12-hour intervals and the patient should be carefully monitored to ensure that an adequate suppression of ventricular ectopy is maintained. The maximum single dose that should be utilized is 75 mg.

Use of higher initial doses and more rapid dosage adjustments have resulted in an increased incidence of proarrhythmic events particularly during the first few days of dosing, therefore, a loading dose is not recommended.

Although limited experience with the concomitant use of ENKAID and intravenous lidocaine has revealed no adverse effects, there are no formal studies to demonstrate the utility of such combined therapy. Clinical experience on transferring patients to ENKAID from another antiarrhythmic drug is also limited. As a general principle, antiarrhythmic therapy should be withdrawn for two to four plasma half-lives before ENKAID is started. If withdrawing antiarrhythmic therapy is potentially life-threatening, consideration should be given to hospitalization.
Facilities for determining plasma levels of encainide and its metabolites are not readily available and the utility of such measurements in guiding the care of patients has not been demonstrated.

HOW SUPPLIED
Capsules, 25 mg, green and yellow hard gelatin capsule imprinted with ENKAID, 25 mg, Bristol and 732.
NDC 0087-0732-41 Bottles of 100
Capsules, 35 mg, green and orange hard gelatin capsule imprinted with ENKAID, 35 mg, Bristol and 734.
NDC 0087-0734-41 Bottles of 100
Store at room temperature – Protect from temperatures greater than 86°F (30°C).

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